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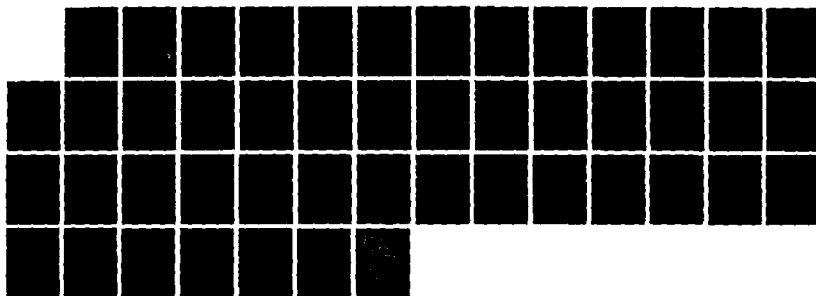
SMALL VOLUME RESUSCITATION OF HYPOVOLEMIC SHOCK(U)  
CALIFORNIA UNIV DAVIS DEPT OF HUMAN PHYSIOLOGY  
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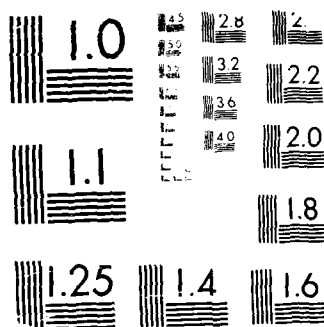
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SMALL VOLUME RESUSCITATION OF HYPOVOLEMIC SHOCK

Annual Report

31 Jan 86 - 31 Jan 87

George C. Kramer, Ph.D.

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## Table 1

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## Foreword

Experimentation on animals is reported. We complied with Guide for the Care and Use of Laboratory Animals, prepared by the Committee on Care and Use of Laboratory Animals, Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. (NIH) 72-73, Revised 1978).

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### Summary

Studies on unanesthetized sheep were performed to evaluate effectiveness of hypertonic saline dextran formulations. Studies on anesthetized rat measured changes in intracellular metabolism of skeletal muscle during shock and resuscitation. Based on presented data we conclude:

Hypertonic saline, 2400 mosm, 6% dextran 70 solution is safe and equally effective if given by central infusion, peripheral vein, or artery.

Hypertonic saline dextran is more effective at maintaining vascular expansion than hypertonic saline hetastarch.

The addition of dextran to hypertonic saline increases the vascular expansion and improves cardiovascular function in a dose response manner.

Hemorrhage has slow acting and varied effects on high energy phosphates of skeletal muscle. Monitoring of skeletal muscle with NMR is unlikely to be a good measure of the effectiveness of different resuscitation regimens.

## 1. Statement of Problem

Recent animal investigations in our lab (1,2,3) and those of others (4,5,6) have established that small volume infusions of hypertonic saline can effectively restore cardiovascular function after hypovolemic shock. It is our overall goal to extend our experience and knowledge of small volume resuscitation. We must establish the most effective way to utilize hypertonic resuscitation and determine its limits and possible dangers. Most important is to better understand the physiologic and biochemical mechanism of its beneficial effects. Our specific aims are:

- \*1) Evaluate the importance of adding colloid to hypertonic resuscitation.
- \*2) Evaluate the possibility of using peripheral vein access for hypertonic resuscitation.
- 3) Determine the effectiveness and safety of multiple bolus injections of hypertonic saline.
- \*4) Use NMR to measure intracellular energy stores during hemorrhage in skeletal muscle, kidney, and liver.
- 5) Use NMR to evaluate the metabolic effectiveness of hypertonic resuscitation regimens.
- 6) Measure the distribution of cardiac output during hypertonic resuscitation.
- 7) Use hypertonic resuscitation in dehydrated animals.

\* indicates work accomplished during year 01



## 2. Background

Basic and clinical research stimulated by World Wars I and II established the basis for current treatment of hypovolemic shock as 1) control of hemorrhage and 2) restoration of vascular volume (7). A hemorrhaged soldier arriving at a field hospital in Vietnam was given definitive care - prompt surgical control of bleeding and intravenous infusions of physiological salt solution and/or blood as needed (8). Despite the availability of effective resuscitation therapy in hospitals exsanguination remained the main cause of mortality, being responsible for 50% of all deaths even with a highly efficient system of rapid helicopter evacuation (9,10). A recent model analysis based on Vietnam casualty statistics concluded "for there to be significant improvement in combat casualty care there must be a renewed emphasis on field medical care, with special attention to management of hemorrhage" (10). Successful field resuscitation has been limited by the large volumes required of solutions of crystalloid (2-4x shed blood volume) and colloid (1 - 1-1/2x shed blood). Logistically feasible field therapies are needed which will reestablish near normal cardiovascular function, and protect against the deleterious metabolic alterations of tissue ischemia.

A novel approach to resuscitation is suggested by the studies of Rocha e Silva and his colleagues (4,5) in which hemorrhaged dogs were successfully resuscitated with a small bolus infusion of hypertonic saline. A 2400 milliosmolar solution of sodium chloride equal in volume to only 10% of shed blood rapidly returned cardiac output and blood pressure to normal (4). These significant and rapidly beneficial effects of hypertonic infusions have been generally verified in our studies of hemorrhage and resuscitation of the unanesthetized sheep (1,2). Improved survival has been demonstrated in anes-

thetized dog by Rocha e Silva and more recently in conscious swine by Traverso et al. (4,6). Resuscitation with equal volumes of 1200 mosm and 4800 mosm sodium chloride were not as effective as with 2400 mosm. The exact mechanisms of hypertonic resuscitation remain undefined but are at least partly due to plasma volume expansion subsequent to a cellular/extracellular fluid shift and a significant reduction in peripheral resistance. In addition, stimulation of a pulmonary osmoreceptor may initiate a reflex decrease in venular capacitance, thus effectively increasing cardiac output to normal levels despite blood volumes less than normal (5). Also, it has been suggested that hyperosmolality either directly or indirectly improves cardiac performance but this also remains to be determined. A better understanding of the relative importance of these mechanisms is required in order to optimize resuscitation regimens.

We have shown that the initial rapid improvement in cardiovascular function is a function of the increased osmolality per se and does not require either sodium or chloride (11). Figure 1 shows a study in which we performed a screening evaluation of the effectiveness of five different hypertonic solutions.

Mean arterial pressure is plotted for baseline conditions, during 2 hours of hemorrhage (blood loss = 40-45 ml/kg) and for 3 hours after a 4 ml/kg bolus of 2400 mosm solutions of sodium chloride (NaCl); sodium acetate-sodium chloride mix 50:50 (Acetate); Glucose; Mannitol-sodium chloride mix 60:40; and sodium-bicarbonate (Bicarb). Clearly all solutions rapidly returned cardiac output to normal levels within minutes of bolus injection. Thereafter, blood pressure slowly declined with all solutions. Hypertonic bicarbonate caused severe alkalosis and was the least effective solution. Hypertonic glucose and mannitol are initially effective, but are associated

with a large diuresis and fluid losses which are substantially greater than with the other solutions. The most effective solution was 2400 mosm saline which caused rapid and full restoration of cardiovascular function, but the improvement was only transitory.

At this time we began to consider the possibility of adding a hyperoncotic colloid to the formulation. We reasoned that the hypertonic sodium chloride would pull water out of the cell while a hyperoncotic colloid would selectively partition this water in the vascular space. This idea was suggested by our earlier work on dextran 70 in burn resuscitation in which we found dextran to be a highly efficient plasma volume expander associated with a good cardiovascular response (12). In a detailed study (Figure 2) we compared a mixture of hypertonic sodium chloride mixed with 6% dextran 70, (HS-Dex) against hypertonic saline alone (HS) and 6% dextran 70 in normal saline (Dex) and no resuscitation. Hypertonic saline-dextran (NaCl-Dex) resulted in significantly higher values of sustained cardiac output, mean arterial pressure, and measured plasma volume while the total peripheral resistance was lower when compared to hypertonic saline alone or dextran alone. In short, while the hyperosmotic solutions caused a large and immediate improvement in cardiovascular function the addition of the dextran was required to sustain the effectiveness.

We believe the improved response with the mixture of dextran and hypertonic saline results from a greater proportion of the extracellular fluid expansion being partitioned into the vascular space. Whether these responses can be improved with different types or amounts of colloid remains to be determined.

We evaluated how the addition of an initial bolus injection of hypertonic saline-dextran affected cardiovascular function and volume requirements of conventional resuscitation (13). Sheep were bled to 50 mm Hg for 3 hours and then randomly selected for a bolus of 200 ml of hypertonic saline-dextran or normal saline. After 30 min (simulation of transport time) all animals were resuscitated with Ringers lactate to return and maintain cardiac output at baseline values. Figure 3, 4 and 5 show changes in mean arterial pressure, cardiac output and oxygen consumption. The data suggests that a single bolus injection of hypertonic saline-dextran can stabilize cardiovascular function and begin payback of oxygen debt during patient transport before conventional large volume therapy is available. While both groups responded well once Ringers lactate infusion was begun, the volumes required in the HS-dextran group were 200-700 ml compared to 1300-3850 ml after the normal saline bolus. After hypertonic saline-dextran, volume requirements were reduced an average of 83%.

We used an anesthetized rat model to examine the effects of hypertonic saline on the cellular/extracellular balance of fluid and electrolytes in skeletal muscle (3). During hemorrhagic shock we found, as reported by others (14), that the membrane potential partially depolarizes as sodium and water enter the cell. A small volume bolus injection of hypertonic saline increased blood pressure and restored cell water and electrolyte content to normal, figure 6. An infusion of a volume of normal saline equal to 8x the hypertonic bolus had less effect on blood pressure and caused no improvement in cellular variables. The above data suggest that part of the explanation for the improved cardiovascular response and higher survival rate after hypertonic resuscitation may be related to improved cellular function and metabolism.

To examine the hypothesis of improved cellular metabolism, after hypertonic resuscitation, we are currently using topical nuclear magnetic resonance (NMR) as a means of non-invasive, in vivo, monitoring of intracellular high energy phosphates (15,16). We monitored cellular metabolism in rat skeletal muscle during shock and small volume resuscitation.

The clinical potential of hypertonic resuscitation and the importance of the added dextran was underlined by recent research completed by Peter Maningas at the Army's Letterman Institute of Research (17). Dr. Maningas compared small volume resuscitation (10 ml/kg) with 4 different formulations in a survival study conducted on severely hemorrhaged unanesthetized swine. Pigs were rapidly bled of 2/3 of their blood volume in 15 minutes. Non-resuscitated animals had a 100% mortality within an hour. Animals were resuscitated with normal saline, hypertonic saline alone, dextran 70 in isotonic saline and the mixture of hypertonic saline + dextran 70. Long term survival was 10% with normal saline, 60% with hypertonic saline, 70% with dextran alone and 100% with hypertonic saline dextran. The protocol was then repeated with the smaller volumes we had used in our published studies (2,11), 4 ml/kg, and there was still better than 90% survival with hypertonic saline-dextran.

James Holcroft has begun the first clinical trials of HSD by treating hemorrhaged patients serviced by the University of California Davis Medical Center's Life Flight Helicopter. Peter Maningas, in collaboration with Ken Mattox and Paul Pepe at Ben Taub Hospital, Houston, has begun clinical trials of hypertonic saline/dextran in a pre-hospital setting as a treatment for penetrating trauma. Preliminary data from these clinical trials is encourag-

ing and suggest that 250 ml of 7.5% sodium chloride/6% dextran 70 normalizes blood pressure and reduces mortality in severely hemorrhaged patients. We are encouraged by the success of the clinical trials and we hope that our continuing animal studies will lead to better resuscitation regimens.

### 3. Rationale

The overall rationale of our study is to evaluate the efficacy and safety of small volume hypertonic resuscitation in experimental animals. Specifically, we will quantitate the cardiovascular response and metabolic response of vital organs during shock and after therapy with different hypertonic formulations and resuscitation regimens. We believe that these experiments will establish potential clinical therapeutic regimens. It is our hope that these regimens will provide field corpsmen with a logistically feasible and effective means to stabilize cardiovascular function in wounded soldiers until definitive care at a field hospital can be provided.

#### 4. Experimental Methods

All experimental procedures outlined below have been previously used by the investigators. Dr. Kramer has been using the unanesthetized sheep preparation since 1980 (1,12) the anesthetized rat model since 1982 (3). Our laboratory is well equipped for aseptic survival surgery and cardiovascular monitoring of unanesthetized and anesthetized animals.

Sheep were used to study the cardiovascular responses to different resuscitation regimens, examine the effects of vagal blockade, measure the distribution of cardiac output, and to evaluate the safety of peripheral vein injections of hypertonic solutions. Sheep were anesthetized with halothane/nitrous oxide for placement of silastic catheters in the thoracic aorta and vena cava and a Swan Ganz thermodilution catheter in the pulmonary artery. Experiments on awake sheep were performed 4-7 days after surgery. Sheep offer several advantages. They are a relatively inexpensive large animal and are easy to study in the unanesthetized state. The awake sheep's cardiovascular response to hemorrhage and resuscitation is similar to man (7), and its response is more applicable than those measured in anesthetized animal preparations. At a blood pressure of 60 mm Hg and lower sheep lie down in their cages. They experience no apparent pain during hypotension, are generally lethargic but conscious for the entire experimental protocol. Almost all sheep experiments consisted of measurements made during a 2 hr baseline period; 2-3 hrs of hemorrhagic hypotension (50 mm Hg) maintained by bleeding without reinfusion, and 2-4 hrs of resuscitation and follow-up.



Rats were used for in vivo monitoring of intracellular high energy phosphates of skeletal muscle. The low cost of rats allowed the many experiments required to establish statistical significance in survival studies, while their small size allowed them to fit into the topical NMR for non-invasive monitoring. Rat experiments typically consisted of a baseline period, 60-90 minutes of hemorrhage (40-50 mm Hg) and a post resuscitation period.

Measured Variables:

Sheep: Pressures of the aorta, pulmonary artery, pulmonary wedge and right atrium were measured with P23 Gould transducers. Pressures, ECG and heart rate were monitored on a multi-channel strip chart recorder. Cardiac output was determined by thermal dilution using an Edwards Cardiac Output Computer. Arterial blood gases and pH were measured with an Instrumentation Laboratories Blood Gas Analyzer. Arterial and mixed venous oxygen content were determined on an Instrumentation Laboratories Co-oximeter. Oxygen consumption was calculated as the average cardiac output times the difference in A-V oxygen content. Urine output was determined by continuous collection from a Foley retention catheter. Plasma and urine concentrations of  $\text{Na}^+$ ,  $\text{K}^+$  and  $\text{Cl}^-$  as well as total osmolality were measured by flame photometry, acid titration and freezing point depression respectively. Lactate was measured on protein precipitated blood samples with enzyme assay. Creatinine clearance was determined by enzymatic assays of blood and urine. Plasma volume was measured as the distribution volume of Evans Blue dye.

Rat: Arterial and central venous pressure and heart rate were determined by placement of PE 50 catheters and pressure monitoring. Intracellular metabolic status was evaluated by using topical NMR to monitor relative levels of phosphocreatine, ATP, inorganic phosphate and pH in skeletal muscle. HPLC and enzymatic assays on excised tissue samples were performed to quantitate high energy phosphates, lactate and ammonia and other metabolites.

## Results:

Peripheral Vessel Injections - efficacy and safety: After a 2 hour baseline period animals were hemorrhaged to maintain mean arterial pressure at 50 mm Hg for 2 hours (blood loss equal to 38 - 46 ml/kg). Thereafter each animal was treated with 200 ml of 7.5% hypertonic saline - 6% dextran 70 given by a 2 minute infusion into either the right atrium (RA), cephalic vein (CV) or femoral artery (FA). Six experiments were performed for each route of infusion. Figures 7, 8 and 9 show mean arterial pressure, cardiac output, and measured plasma volume for all 3 groups.

Histological examination of peripheral vessels sampled immediately or several days after infusions showed no significant pathology. We conclude that small volume resuscitation with hypertonic saline-dextran is equally effective and safe if given by either central or peripheral vascular catheters.

Comparison of Different Colloids - hypertonic saline dextran versus hypertonic saline hetastarch: We compared the effectiveness of small volume resuscitation of 2400 mosm hypertonic saline-6% dextran 70 versus 2400 mosm hypertonic saline-6% hetastarch. Cardiovascular measurements were made during baseline and 2 hours of hemorrhage hypotension and for 2 hours after a 200 ml bolus infusion of each test solution. Both solutions caused improvement in cardiac output and blood pressure - but the response in blood pressure, figure 10, and cardiac output, figure 11, was significantly better with the dextran formulation. To determine the reason for the difference we measured plasma colloid osmotic pressure using a membrane oncometer and the plasma levels of dextran/ hetastarch using anthrone assay. While the initial serum

concentrations were similar for dextran and hetastarch, we found that the hetastarch is more rapidly cleared by the circulation. In addition, on a per gram basis dextran exerted nearly twice the colloid osmotic pressure of hetastarch.

#### Importance of Added Colloid in Small Volume Hypertonic Resuscitation

- Comparison of 6 versus 24% dextran: To further evaluate the importance of the added dextran to the hypertonic saline, we compared resuscitation with 3 solutions - 2400 mosm hypertonic saline alone (HS-0% Dex), hypertonic saline with 6% dextran 70 (HS-6% Dex) and hypertonic saline with 24% dextran 70 (HS-24% Dex). After a 2 hour period of hemorrhagic hypotension we resuscitated with 100 ml ( $\sim 2$  ml/kg) of test solution. We used these smaller volumes because our previous studies had established that 200ml of hypertonic saline/6% dextran resulted in near normal restoration of blood pressure and cardiac output. We reasoned that with the smaller volumes, we were more likely to establish differential responses.

Results of 6 experiments each are shown for arterial pressure, cardiac output, hematocrit and blood volume expansion in figures 12, 13, 14 and 15. Results clearly show a dose response effect due to the added dextran. The blood volume expansion and the cardiovascular response are both proportional to the amount of dextran given.

#### Metabolic Changes in Skeletal Muscle during Hemorrhage and Resuscitation

- NMR monitoring of high energy phosphates: We used tissue biopsies and topical NMR to monitor intracellular metabolism of skeletal muscle during shock and resuscitation. Table shows NMR measured changes in phosphocreatine (PCr), inorganic phosphorous (Pi), ATP and intracellular pH of biceps femoris

muscle after 60 minutes of severe hemorrhage (MAP = 40-50 mm Hg) in anesthetized rat. Figure 16 shows typical phosphorous spectra during baseline and late hemorrhage. The appearance of an additional sugar monophosphate peak (arrow) occurred in late hemorrhage and its occurrence seemed to coincide with the fall in intracellular pH.

To substantiate these results and to identify the compound responsible for the new peak we measured phosphorous and other metabolites in freeze clamped samples of skeletal muscle from 6 control rats and the 6 shock rats used for NMR measurements, table 2. The difference in PCr and ATP confirm our NMR measurements. Also, the data suggests that glucose 6-phosphate is the sugar monophosphate peak which appears in late shock.

In another series of experiments we used topical NMR to monitor changes in NMR during 90 minutes of hemorrhagic hypotension, 55 mm Hg, and after resuscitation. Lactated Ringers was infused for resuscitation in a volume sufficient to restore mean arterial pressure greater than 80 mm Hg, but a volume not to exceed 4x shed blood volume. After resuscitation rats were monitored for 60 minutes. Five of the 10 rats died during the resuscitation. Thus, experiments were retrospectively divided into a survivor group (n = 5) and a non-survivor group (n = 5). Figures 17 and 18 show average response of mean arterial pressure, ATP, intracellular pH, PCr and Pi. After 90 minutes of shock there was no statistical difference between survivors and non-survivors for arterial pressure, levels of ATP, and pH, while Cr-P was slightly higher in the survivors and Pi was slightly lower. In the post resuscitation period there was consistent improvement in the metabolic status for all survivors, while the non-survivors had a continued deterioration. This trend was particularly evident for Pi which continued to increase in every case in non-survivors but always declined in survivors, figure 19.

Unfortunately, because of the wide variance of responses we were not able to show any consistent beneficial or deleterious effects with hypertonic resuscitation compared to isotonic. We believe that skeletal muscle which exhibits slow and varied metabolic changes during hemorrhage is not the best organ to monitor effectiveness of resuscitation regimens. We expect more useful results using NMR to monitor organs with a higher basal metabolism, e.g. kidney and liver.

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TABLE 1.

Changes in high energy phosphates in skeletal muscle of  
rats subjected to severe hemorrhagic hypotension.

	PCr	Pi	ATP	pH
Baseline	100%	100%	100%	7.08 $\pm$ 0.05
Hemorrhage	67 $\pm$ 10%	274 $\pm$ 26%	89 $\pm$ 10%	6.92 $\pm$ 0.10

TABLE 2

Difference in skeletal muscle contents of  
six control and six rats hemorrhaged for 60 minutes.

	<u>Control</u> (n = 6)	<u>Shock</u> (n = 6)
	umol/gm Dry Weight	
ATP	16.75 $\pm$ 0.77	14.92 $\pm$ 1.18
AMP	0.81 $\pm$ 0.12	0.92 $\pm$ 0.14
IMP	0.20 $\pm$ 0.03	1.36 $\pm$ 0.27
Phosphocreatine	54.33 $\pm$ 4.04	25.88 $\pm$ 4.94
Lactate	5.03 $\pm$ 0.38	37.16 $\pm$ 4.72
Pyruvate	0.39 $\pm$ 0.12	0.33 $\pm$ 0.05
Ammonia	1.35 $\pm$ 0.21	4.21 $\pm$ 0.54
Glutamate	5.65 $\pm$ 0.68	1.58 $\pm$ 0.28
$\alpha$ - Ketoglutarate	0.17 $\pm$ 0.05	0.12 $\pm$ 0.04
Glutamine	11.33 $\pm$ 1.11	14.54 $\pm$ 1.34
Glucose-6-phosphate	0.77 $\pm$ 0.17	10.90 $\pm$ 1.30
Glucose-1-phosphate	0.003 $\pm$ 0.003	0.34 $\pm$ 0.08

## Legends for Figures

1. Mean arterial pressure measured in 5 groups of unanesthetized sheep during 1 hour of baseline, 2 hours of hemorrhage and for 2 hours after a 4 ml/kg bolus infusion of 2400 mosm/l solutions of 1) NaCl, 2) NaCl-Na Acetate (0.6/0.6 M) mixture, 3) NaCl-Mannitol (0.7/1.0 M) mixture, 4) Na Bicarbonate or 5) Glucose.
2. Cardiac output in 4 groups of unanesthetized sheep during hemorrhage and after bolus infusion with 4 ml/kg of 1) 2400 mosm/l hypertonic saline, 2) hypertonic saline with 6% dextran 70, 3) 6% dextran 70 in normal saline and 4) no infusion.
3. Mean arterial pressure in two groups of unanesthetized sheep treated with 200 ml of 7.5% hypertonic saline - 6% dextran 70 or 200 ml of normal saline. After a 30 minute period of simulated patient transport both groups were given lactated Ringers as needed to maintain cardiac output at its baseline values.
4. Cardiac output in same experiments described in figure 3.
5. Oxygen consumption was reduced during hemorrhage but restored to above baseline after hypertonic resuscitation. Same experiments as described in figure 3.
6. Intracellular contents of water, sodium, potassium and chloride in skeletal muscle of anesthetized rats during control, hemorrhage and after resuscitation with either 2400 mosm/l hypertonic saline (volume = 10% shed blood volume) or 290 mosm/l normal saline (volume = 80% of shed blood volume).

7. Mean arterial pressure in 3 groups of unanesthetized sheep during hemorrhage and after a 200 ml bolus infusion given into either the right atrium, cephalic vein or femoral artery.
8. Cardiac output in same experiments described in figure 7.
9. Measured plasma volume was increased equally regardless of route of administration, same experiments described in figure 7.
10. Mean arterial pressure in two groups of unanesthetized sheep during hemorrhage and resuscitation with either 200 ml of hypertonic saline-6% dextran 70 or hypertonic saline-6% hetastarch.
11. Cardiac output in same experiments described in figure 10.
12. Mean arterial pressure in 3 groups of unanesthetized sheep during hemorrhage and after resuscitation with 100 ml of either 2400 mosm/l hypertonic saline alone, hypertonic saline plus 6% dextran 70 and hypertonic saline plus 24% dextran 70.
13. Cardiac output in same experiments as described in figure 12.
14. Hematocrit measurements in same experiments as described in figure 12.
15. Blood volume expansion calculated from decrease in blood hemoglobin concentration after resuscitation with 100 ml of hypertonic saline alone, hypertonic saline plus 6% dextran and hypertonic saline plus 24% dextran.
16. Representative phosphorous spectrum in skeletal muscle of rats during baseline and hemorrhage.
17. Averaged values of mean arterial pressure, ATP, and intracellular pH of skeletal muscle in anesthetized rats during baseline, hemorrhage and resuscitation with lactated Ringers. Animals that survived longer than 60 minutes of resuscitation are grouped as survivors, those that survived less than 60 minutes are grouped as non survivors.

18. Changes in phosphocreatinine and inorganic phosphorous of skeletal muscle in same experiments as described in figure 17.
19. Levels of intracellular inorganic phosphate in skeletal muscle plotted for the individual experiments described in figure 17.

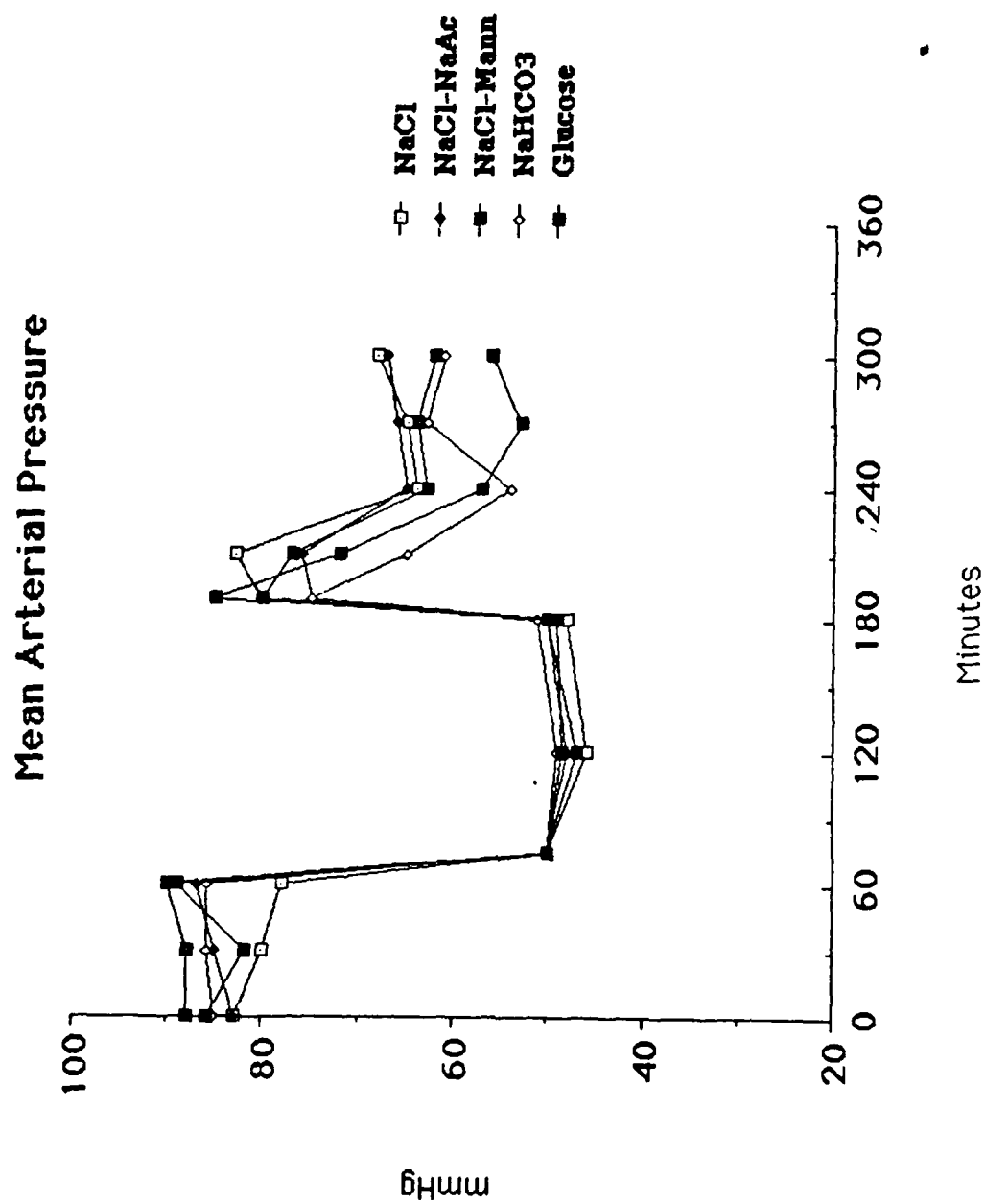


FIGURE 1

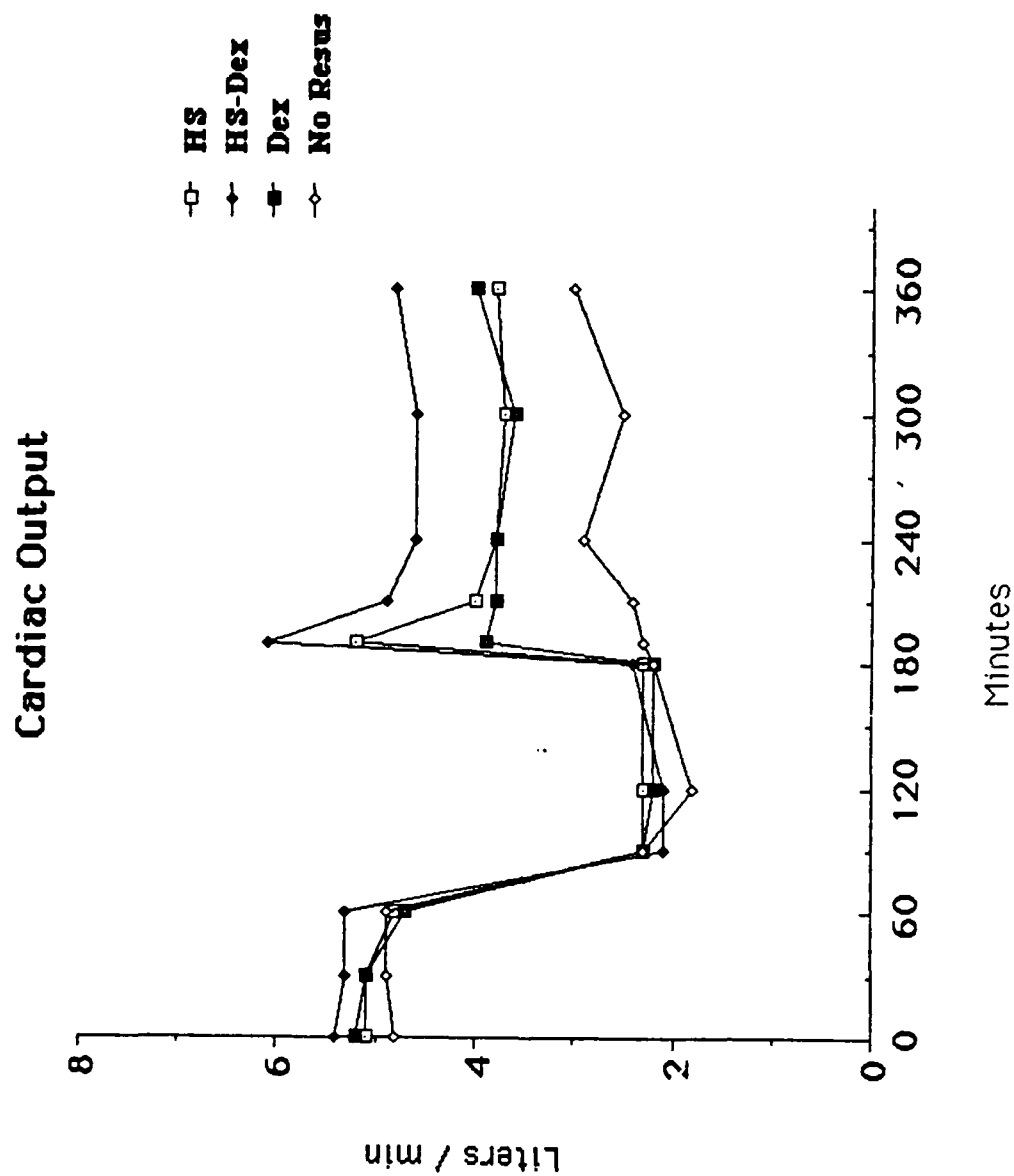


FIGURE 2

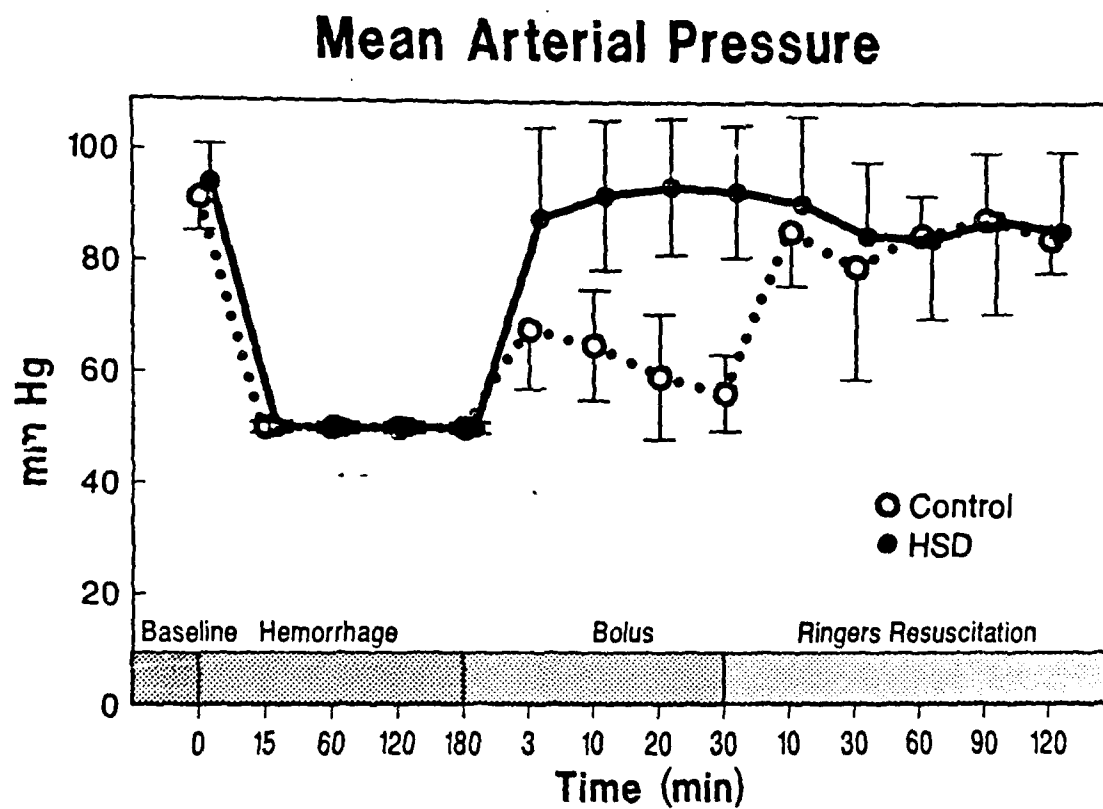


FIGURE 3



## Cardiac Output

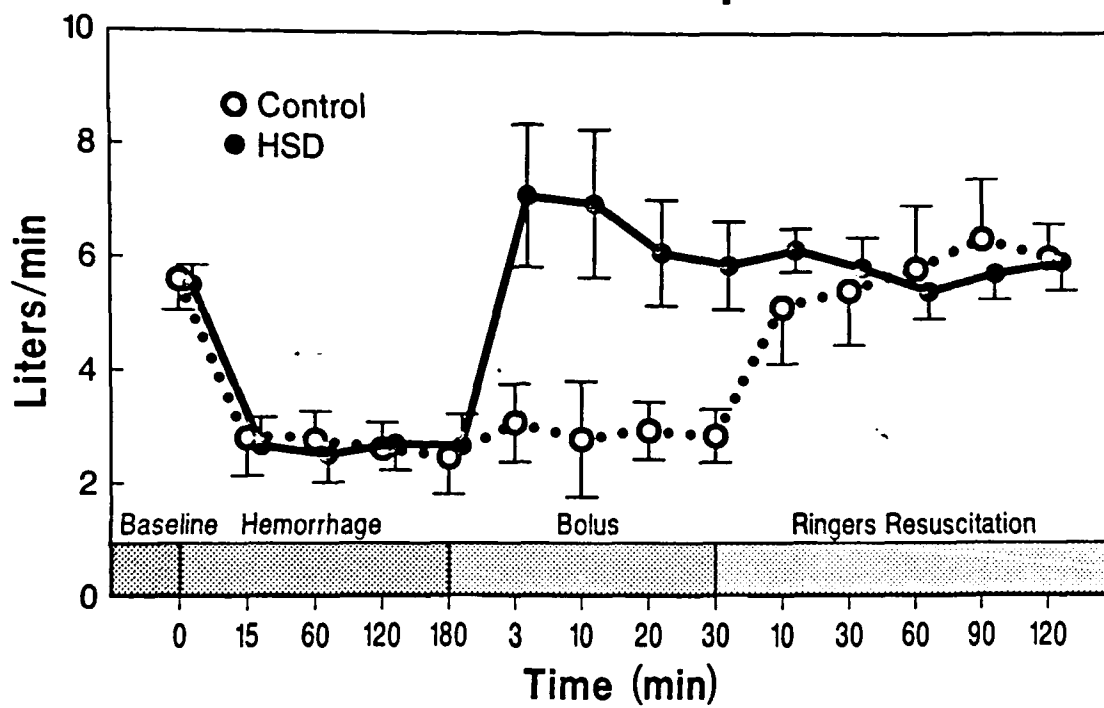


FIGURE 4

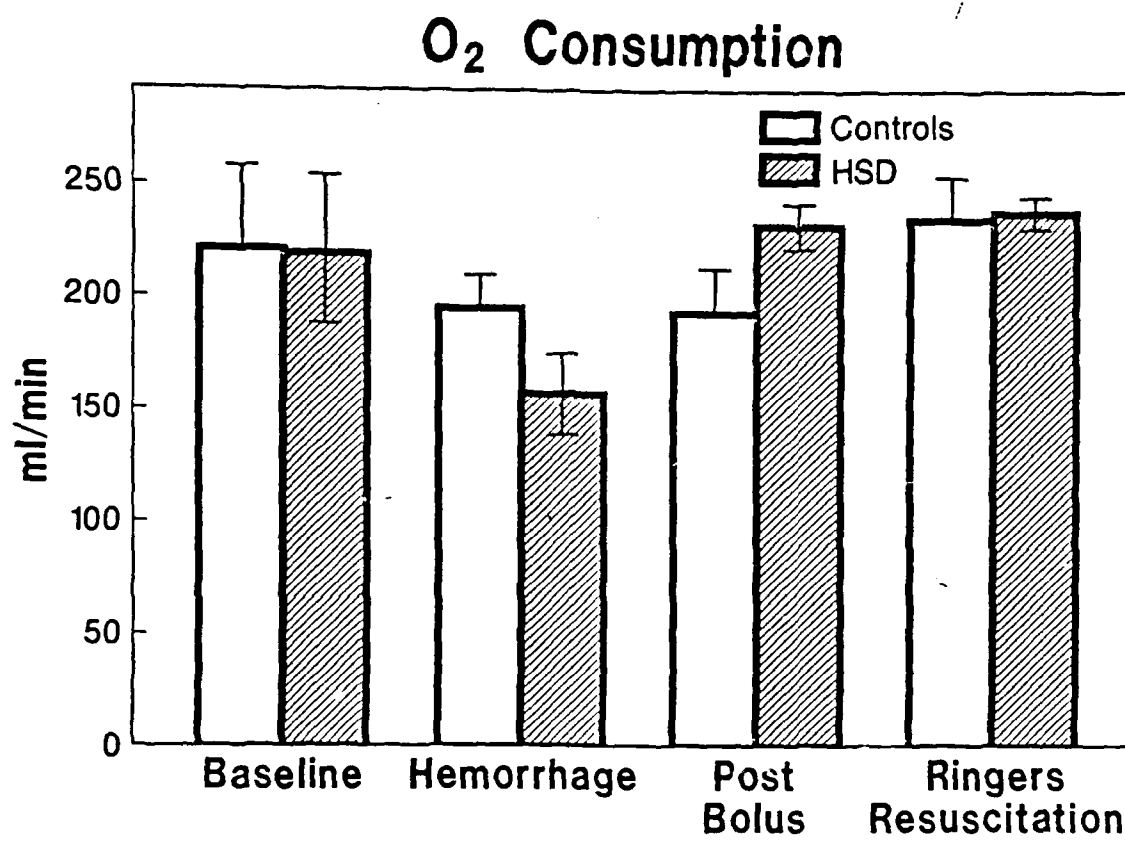


FIGURE 5

## INTRACELLULAR CONTENT

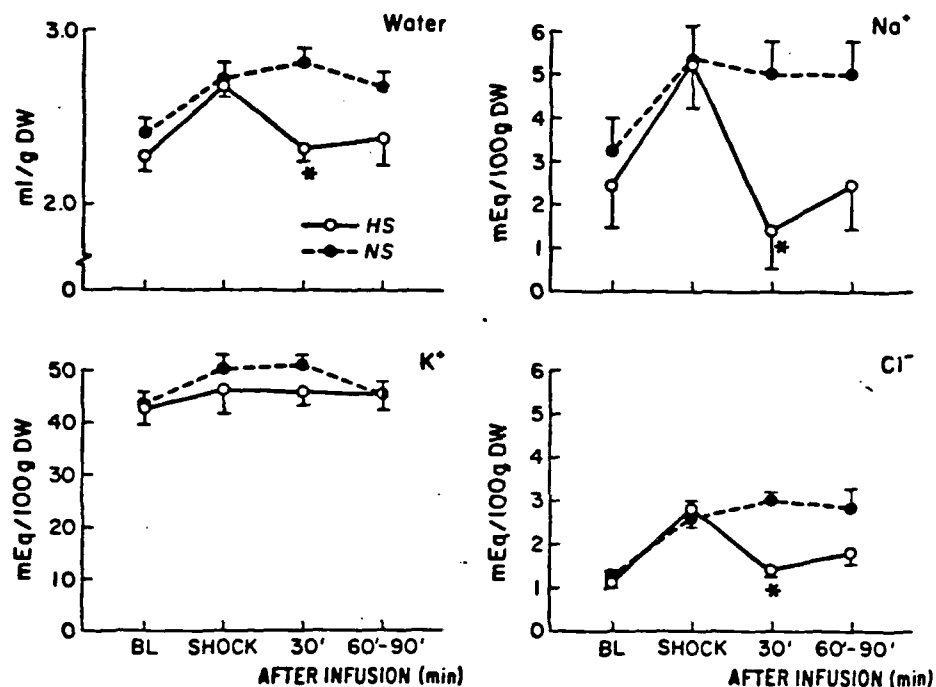


FIGURE 6

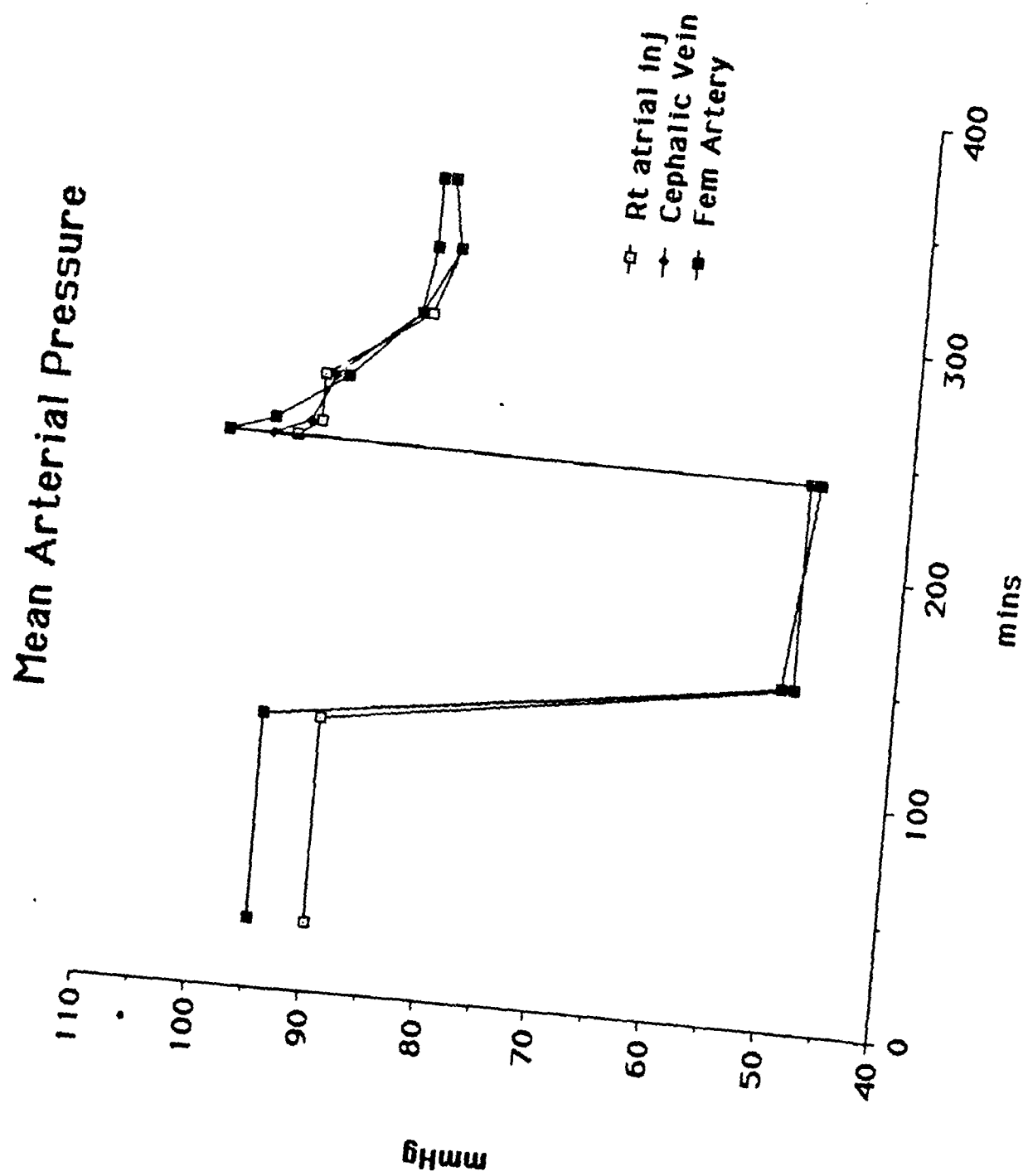


FIGURE 7

## Cardiac Output

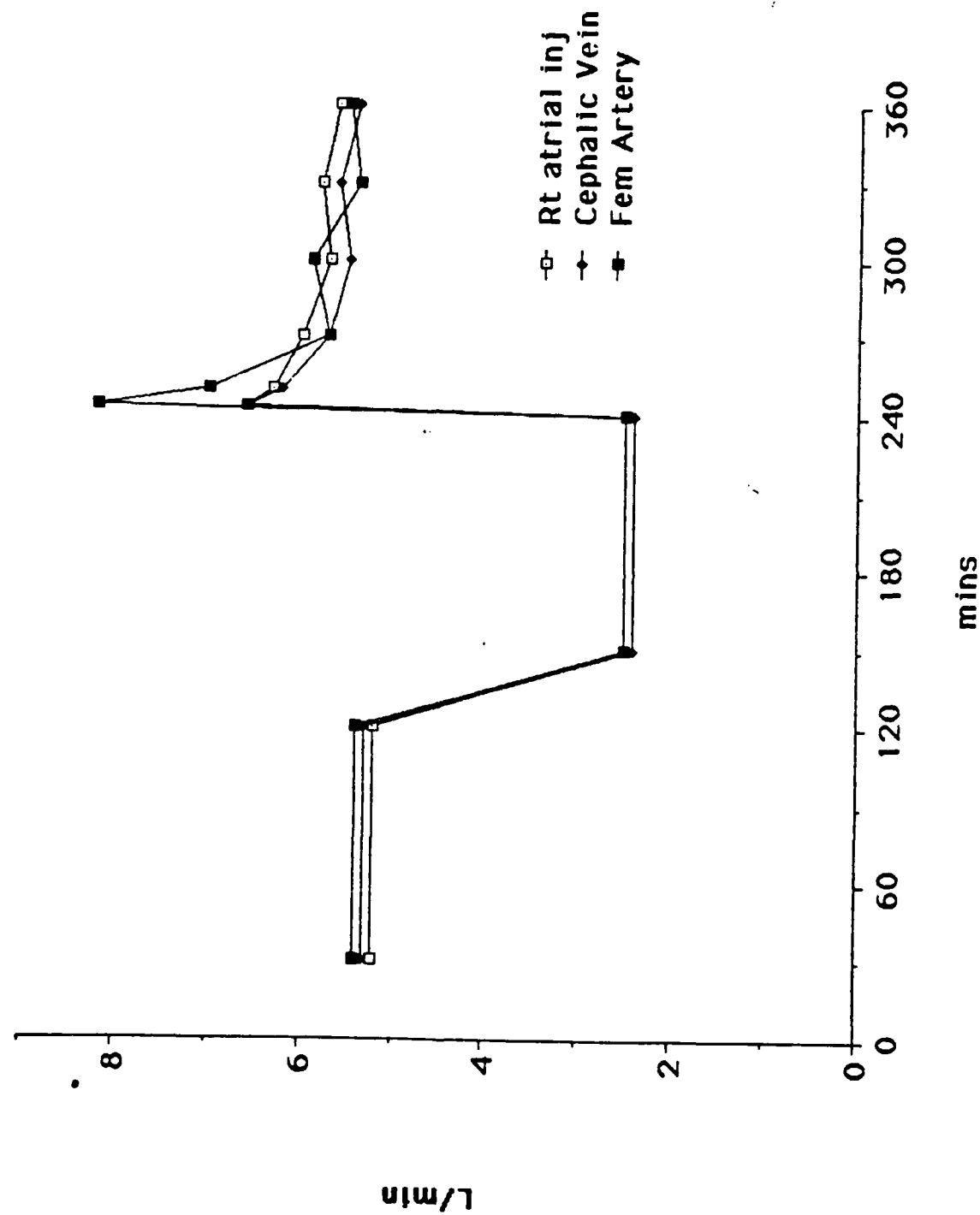


FIGURE 8

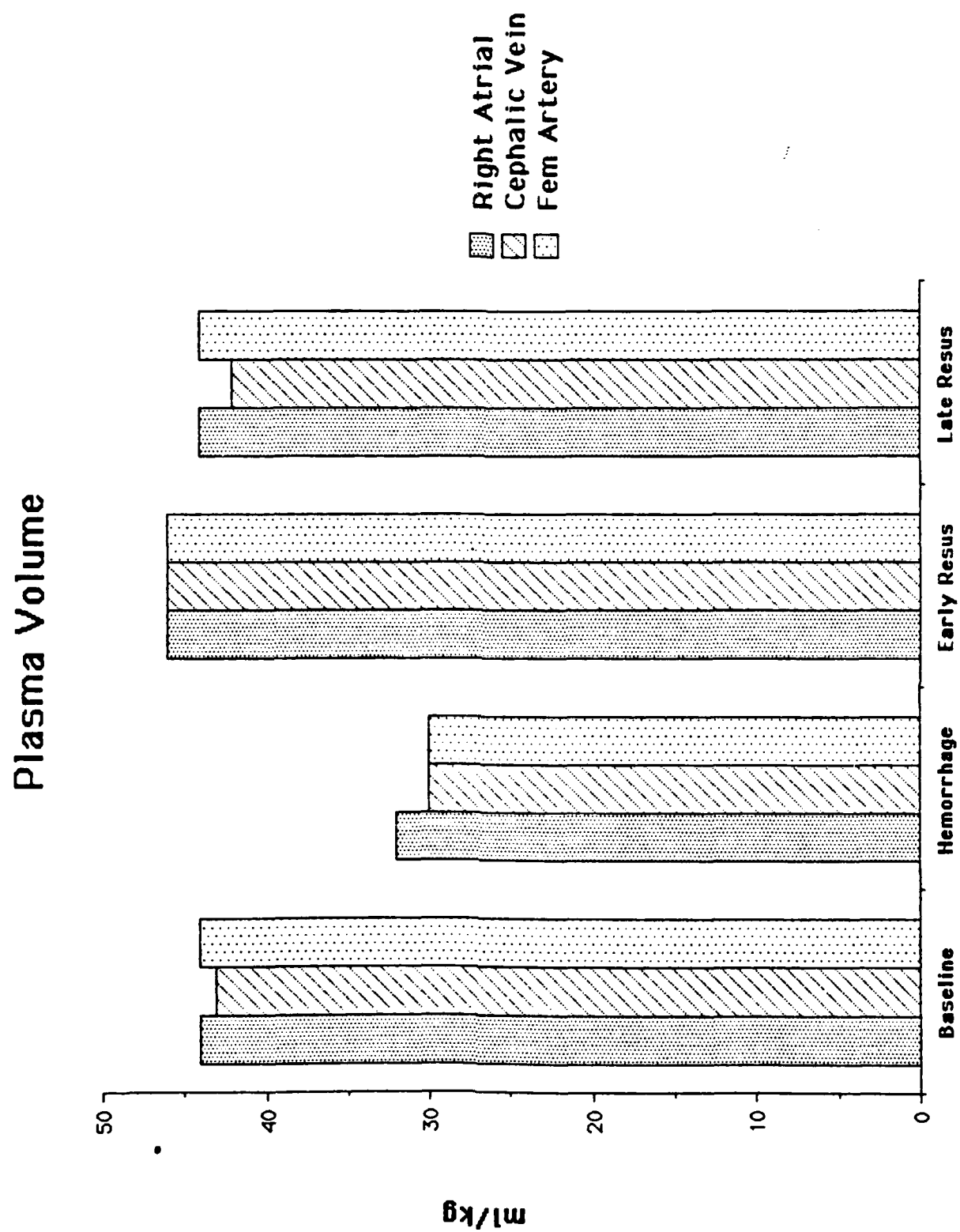


FIGURE 9

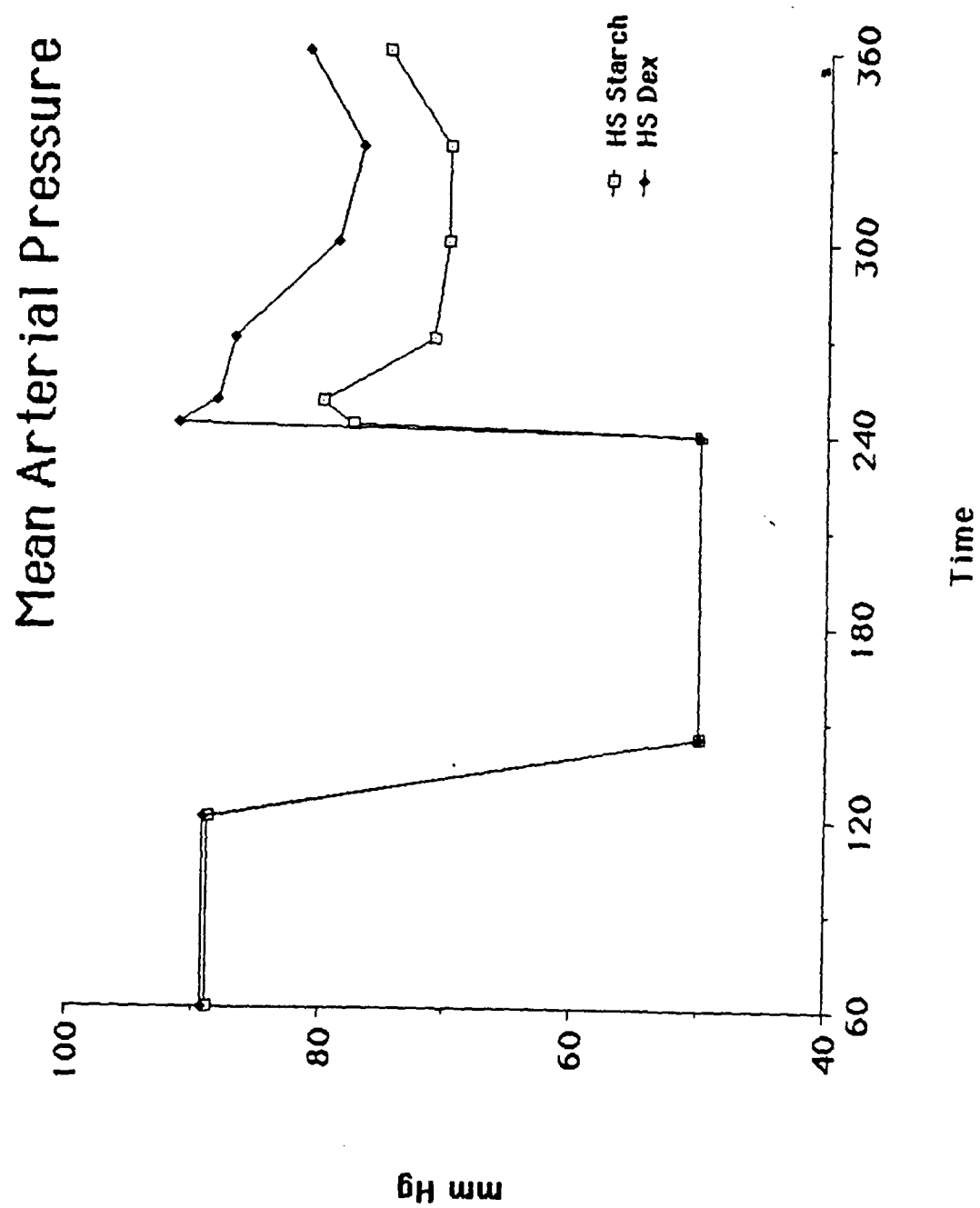


FIGURE 10

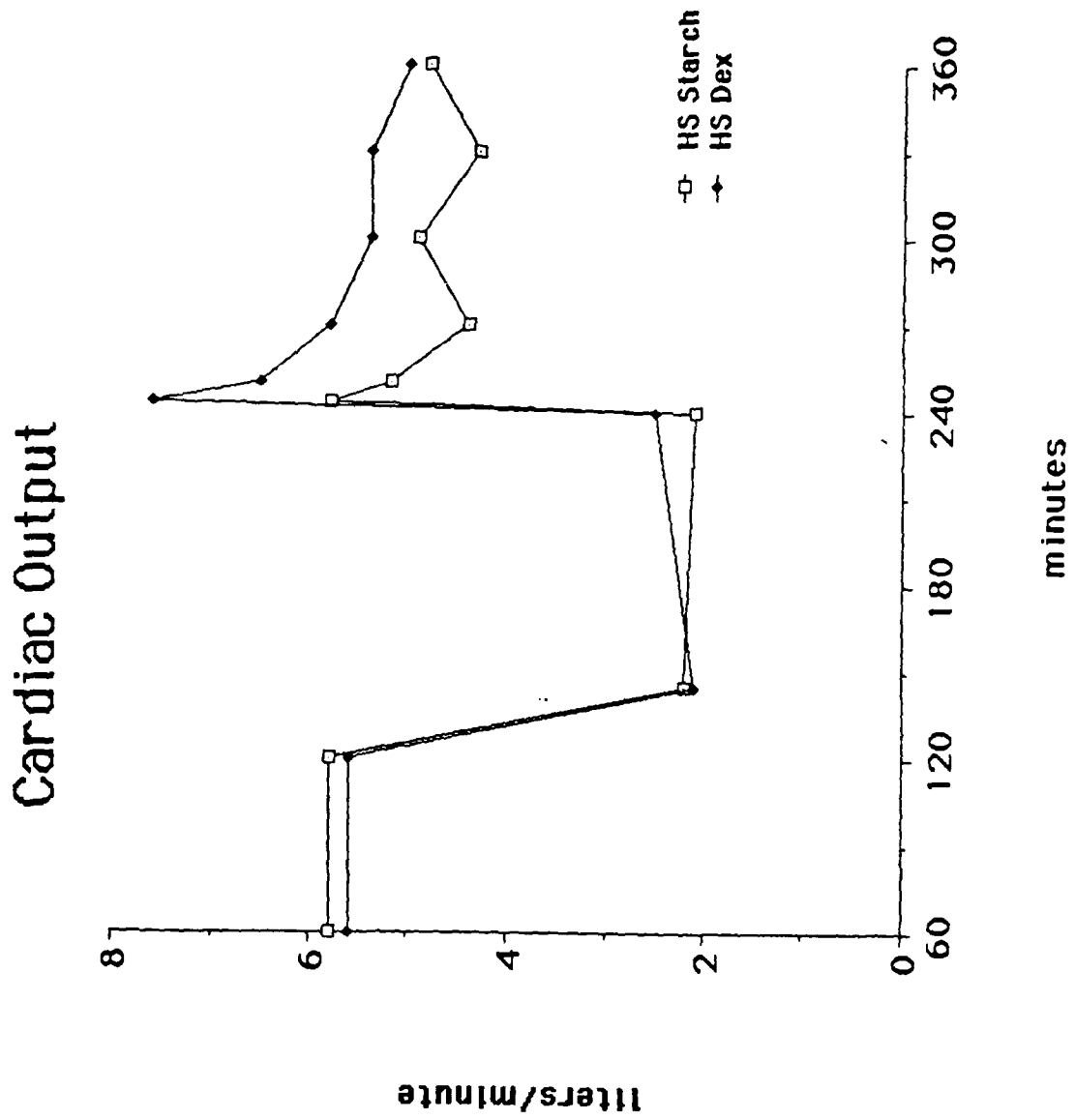


FIGURE 11



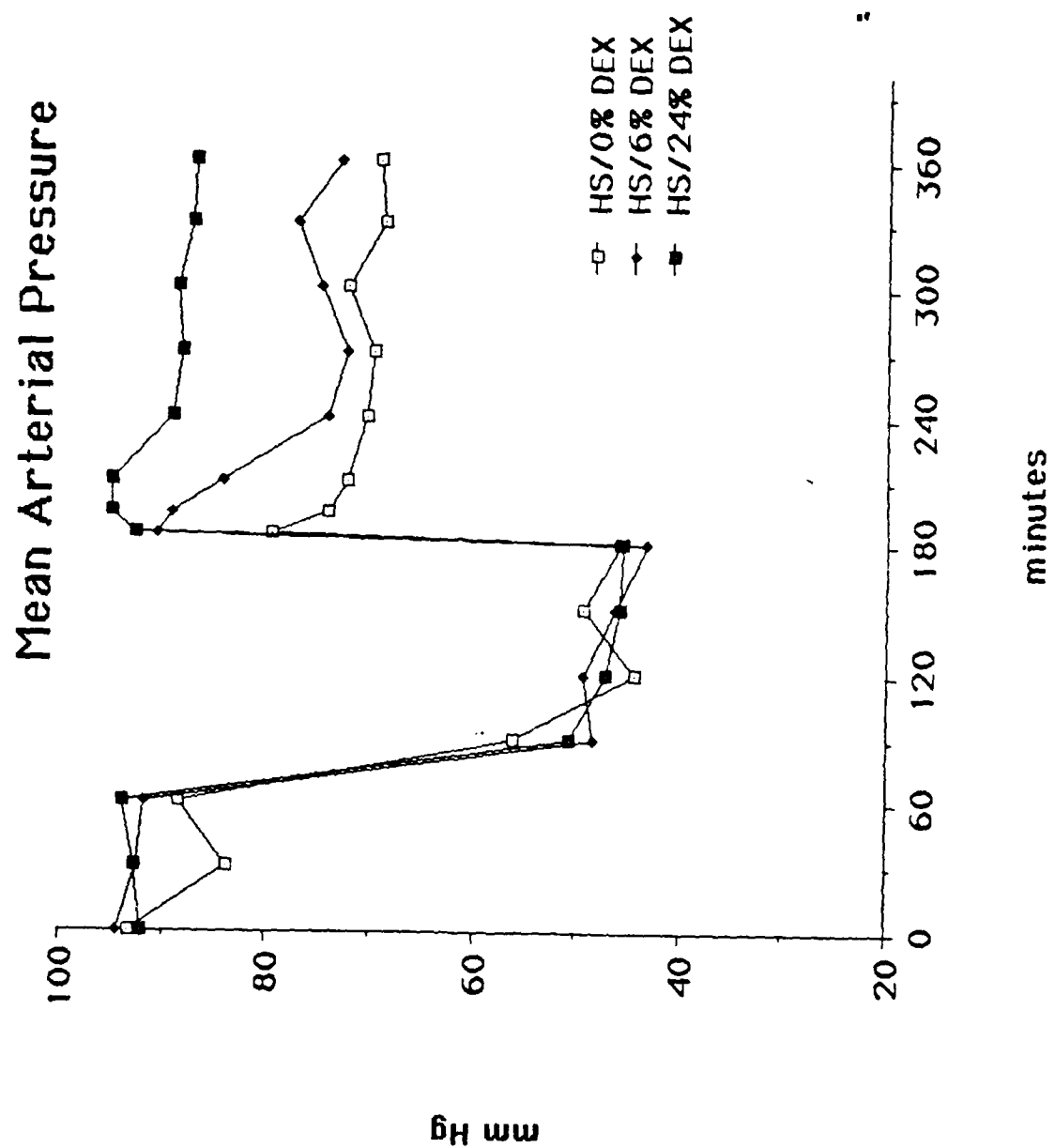


FIGURE 12

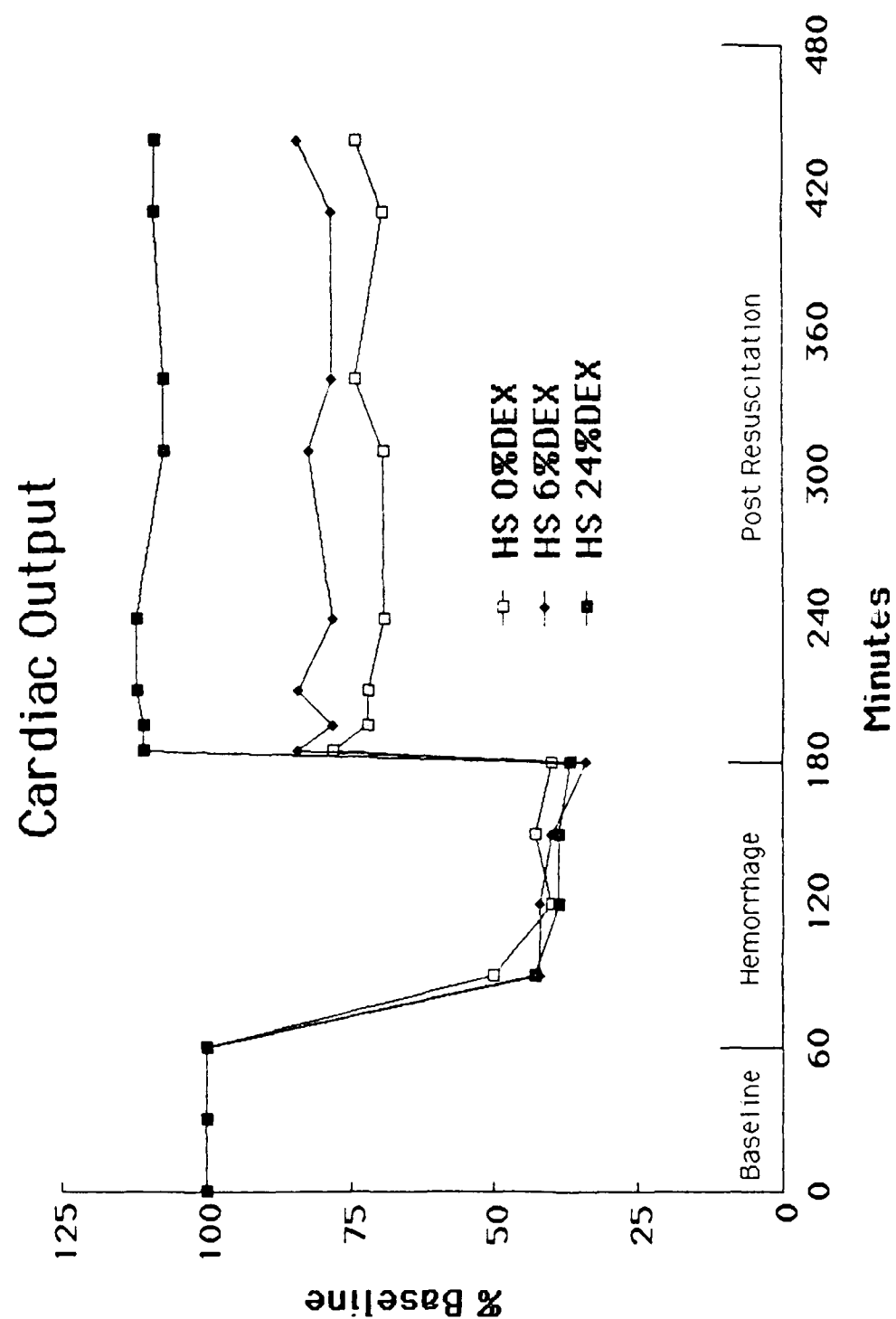


FIGURE 13

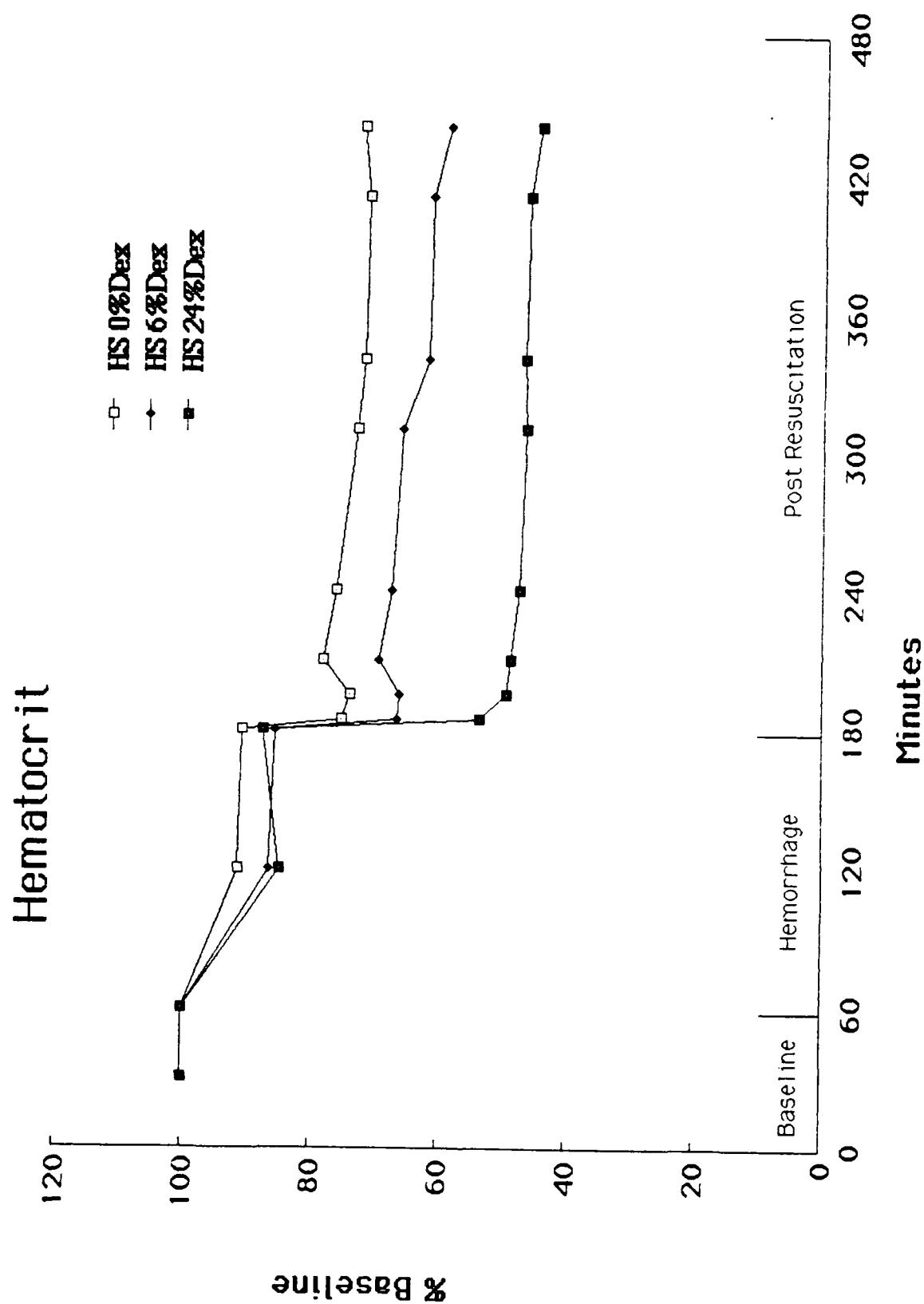


FIGURE 14

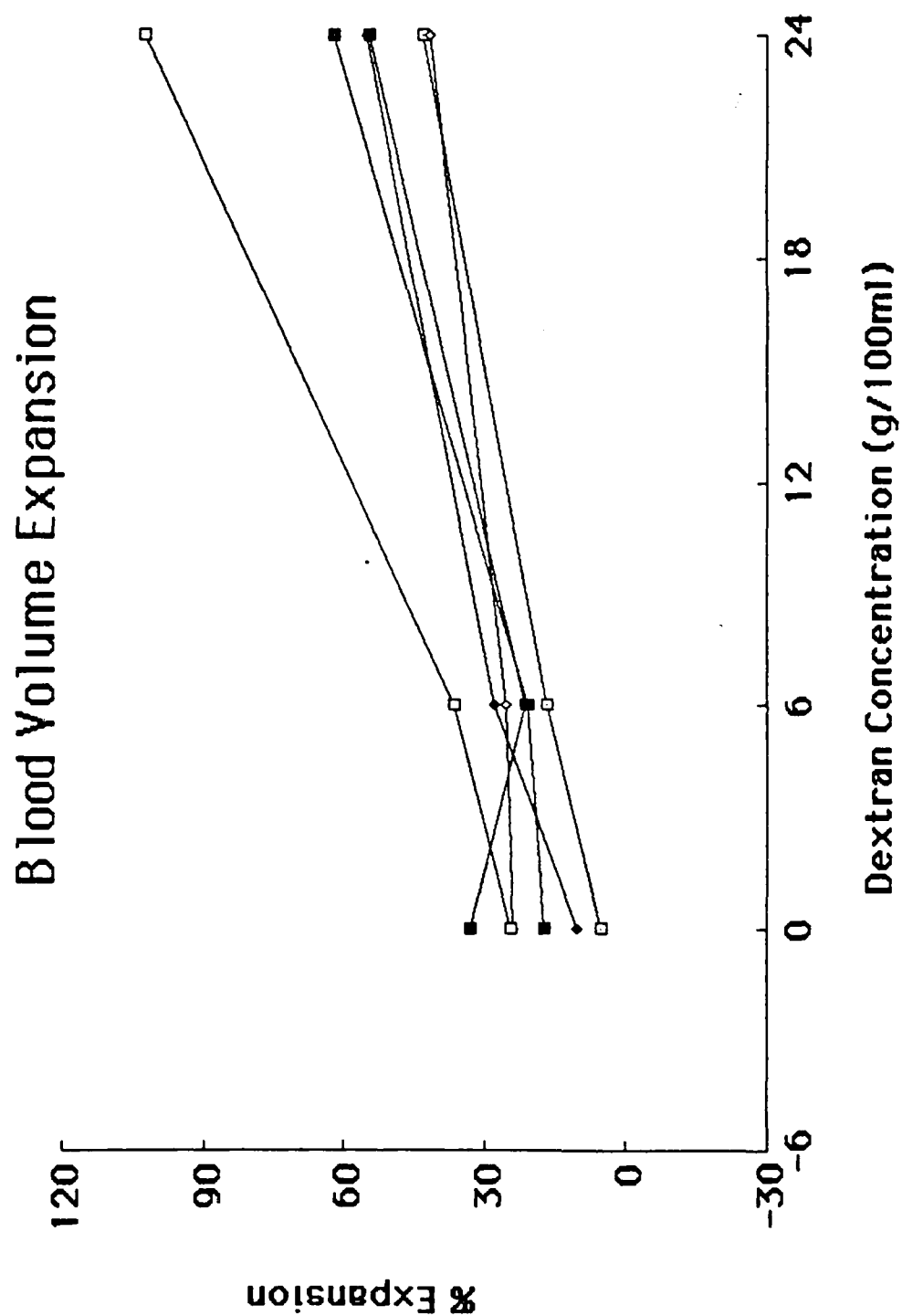


FIGURE 15

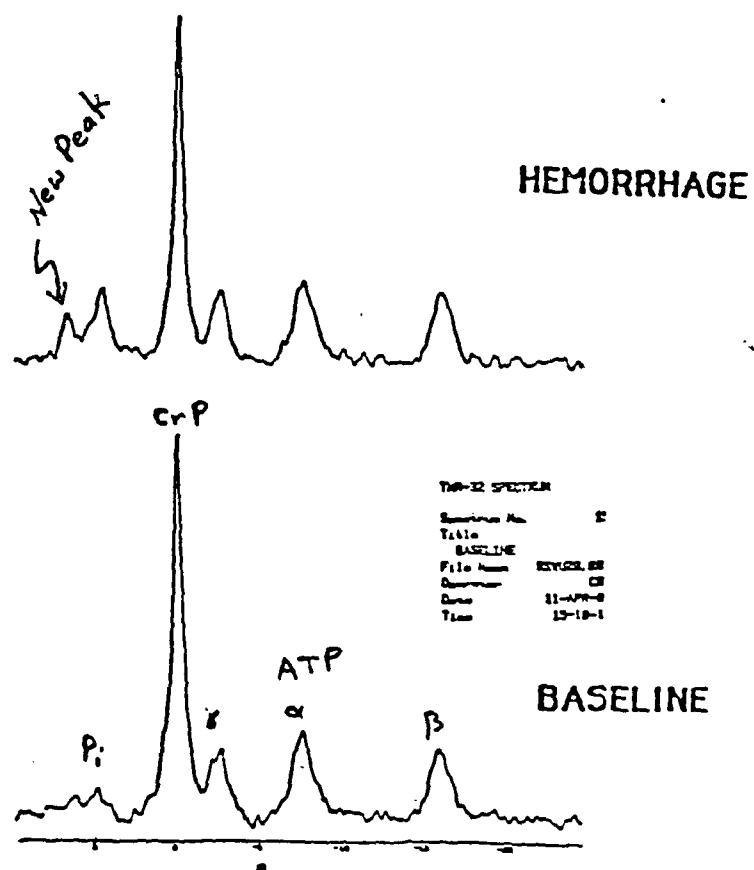


FIGURE 16

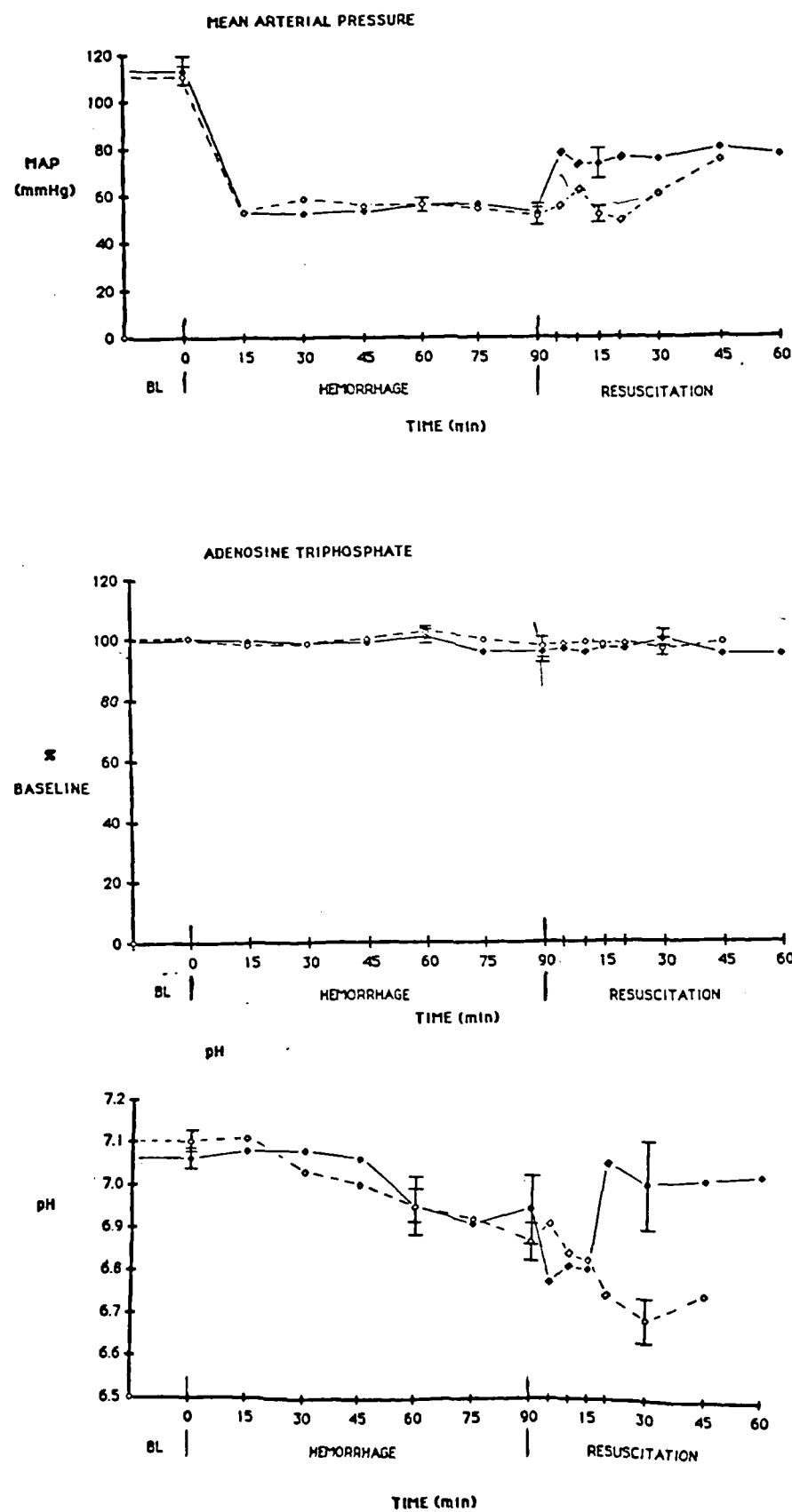


FIGURE 17

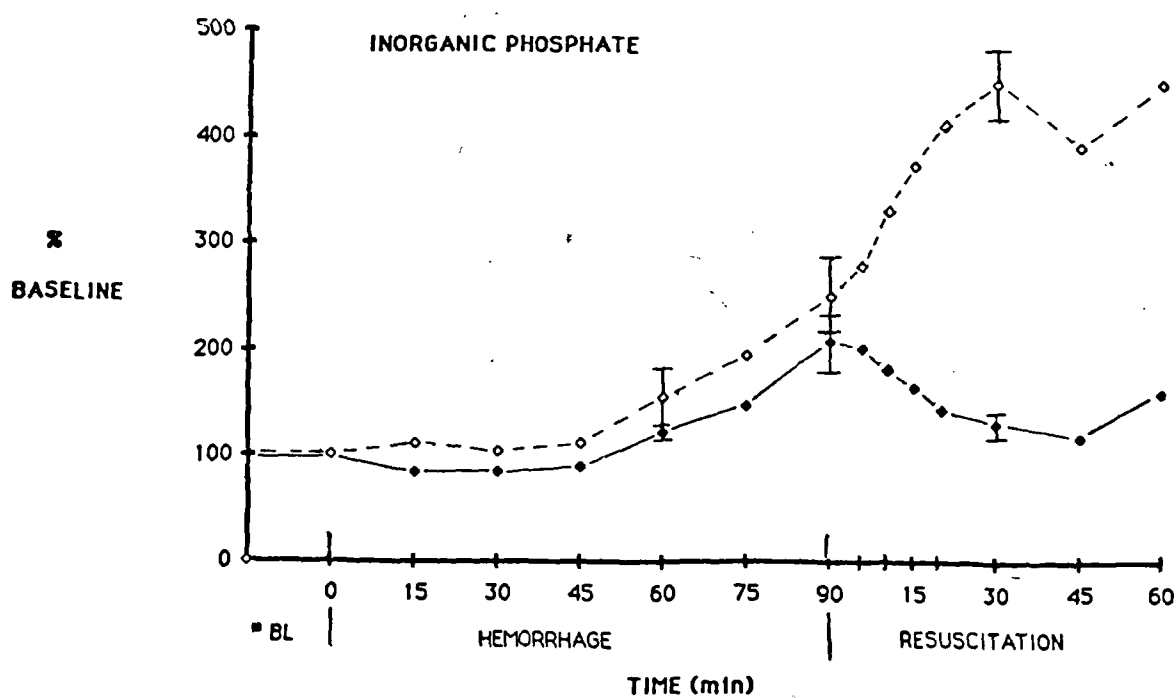
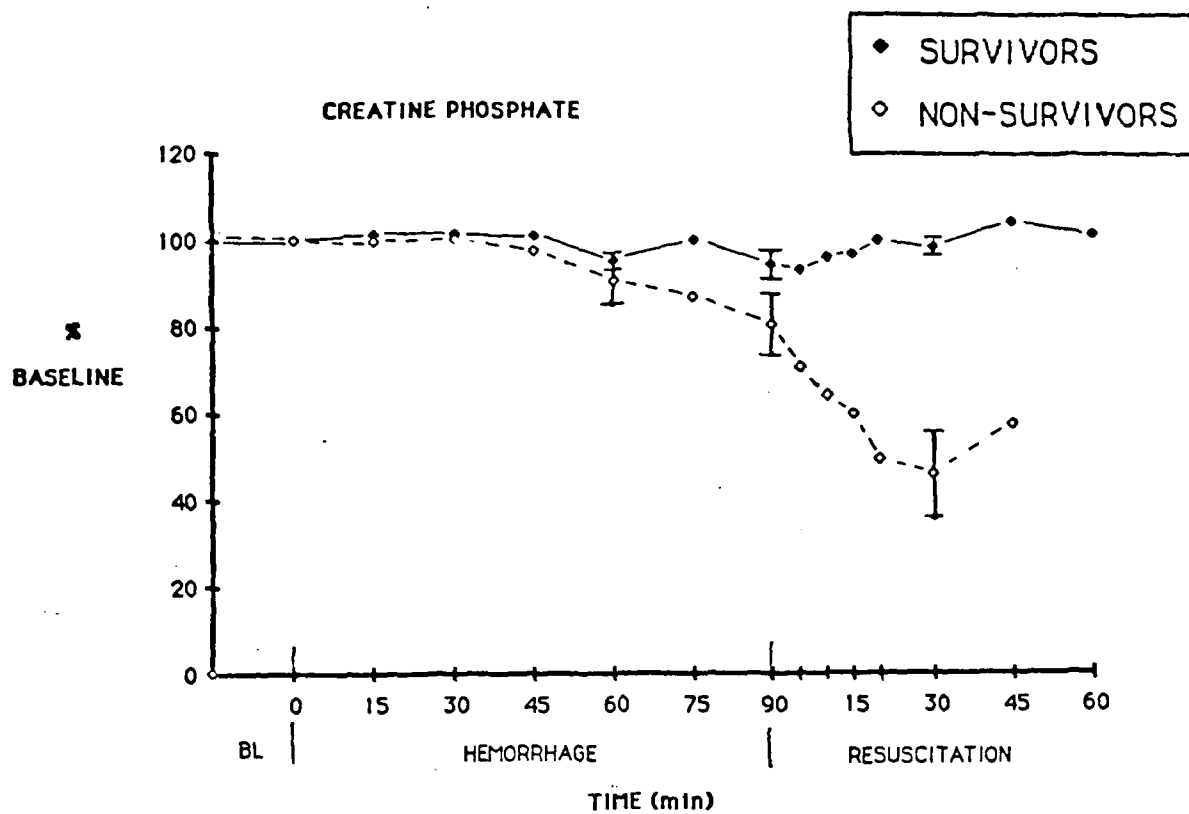


FIGURE 18

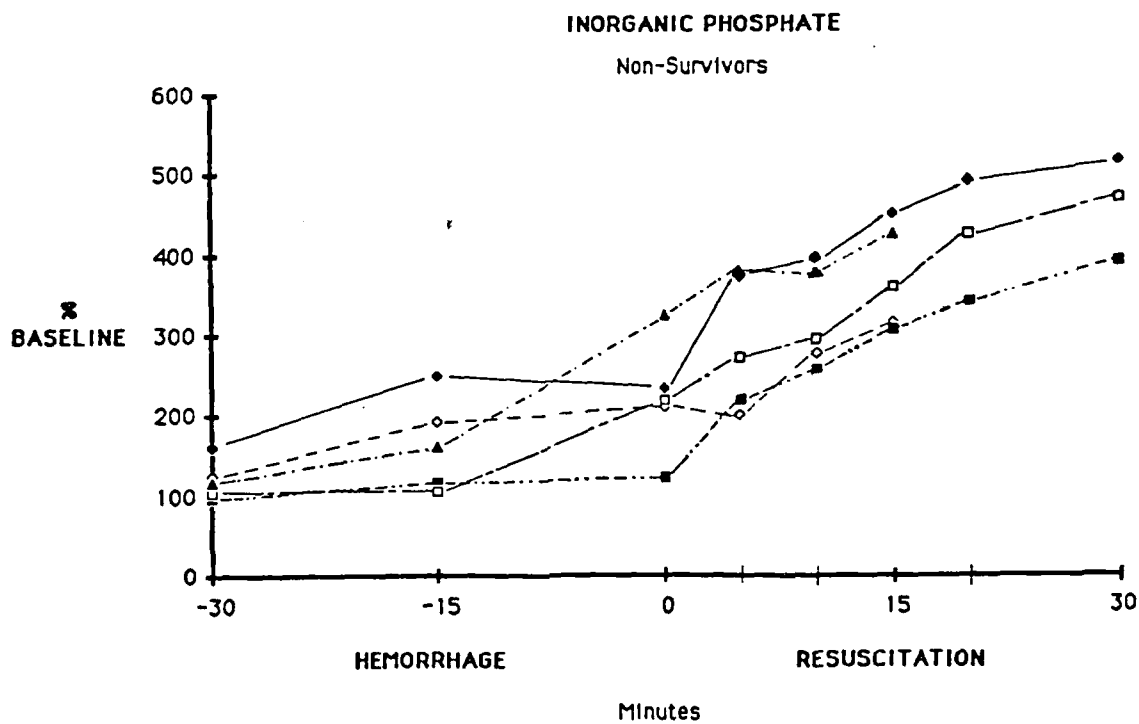
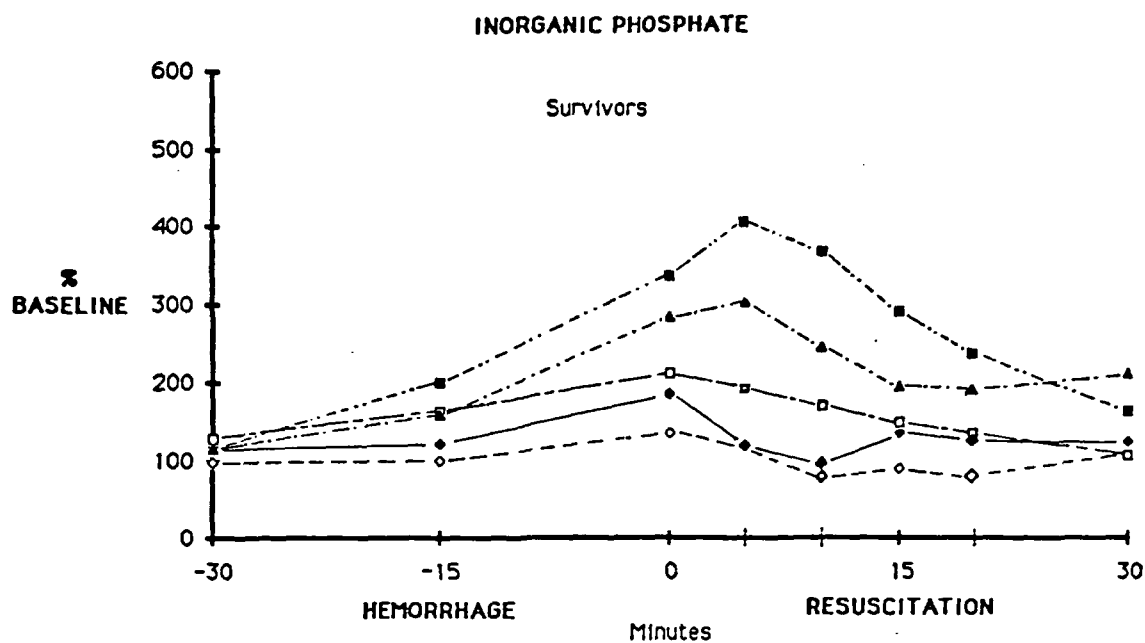


FIGURE 19



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